Molecularly Targeted Therapies in Locally Advanced Non–Small-Cell Lung Cancer

Siddhartha Devarakonda,[1] Daniel Morgensztern,[2] Ramaswamy Govindan[3]

Abstract

Approximately a third of the patients with non-small cell lung cancer (NSCLC) present with locally advanced disease not amenable to curative resection. Concurrent chemoradiation is currently the treatment of choice for these patients. Outcomes in patients with locally advanced NSCLC treated with concurrent chemoradiation are modest at best. No significant progress has been made over the past decade in this subset of patients with NSCLC. Several trials have examined the role of molecular targeted therapies in this setting. We review the results of these trials and present the outline of a proposed prospective clinical trial to evaluate targeted drugs in molecularly selected group of patients with locally advanced NSCLC.

Clinical Lung Cancer, Vol. 14, No. 5, 467-72 © 2013 Elsevier Inc. All rights reserved.
Keywords: Concurrent chemoradiation, Locally advanced NSCLC, NSCLC, Targeted therapy

Introduction

Lung cancer is the leading cause of cancer-related mortality, with an estimated 160,340 deaths in the United States for the year 2012.[1] Approximately 85% of patients with lung cancer have the non–small-cell lung cancer (NSCLC) subtype.[2] Among patients with NSCLC, approximately 25%-30% present with locally advanced non–small-cell cancer, for which concurrent chemotherapy and radiation offer the best potential for cure.[3,4] Even though concurrent chemoradiation significantly improves outcomes in this patient cohort compared with radiation alone or sequential chemoradiation, most of the patients eventually relapse at a distant site. We appear to have reached a plateau in terms of efficacy with currently available cytotoxic chemotherapy regimens that are used in conjunction with thoracic radiation. There is an urgent need to develop novel therapies to improve the outcomes of patients with locally advanced lung cancer.

Over the past decade, several targeted agents have received approval for the management of a wide variety of cancers. Agents that target the epidermal growth factor receptor (EGFR), angiogenesis (vascular endothelial growth factor [VEGF] pathway), and the echinoderm microtubule–associated-like 4-anaplastic lymphoma kinase (EML4-ALK) fusion gene are currently approved for the management of metastatic lung cancer. The efficacy these agents have demonstrated in advanced stage disease led to the design of several trials investigating their role in the management of locally advanced disease.[5–7] We will review the results of clinical trials involving molecularly targeted agents in the treatment of locally advanced NSCLC.

[1]Department of Internal Medicine, St. Luke's Hospital, Chesterfield, MO
[2]Department of Medicine, Yale University, New Haven, CT
[3]Department of Medicine, Washington University School of Medicine, St Louis, MO

Submitted: Jan 5, 2013; Accepted: Mar 19, 2013; Epub: May 14, 2013

Address for correspondence: Ramaswamy Govindan, MD, Division of Medical Oncology, Washington University School of Medicine, 660 S. Euclid, Box 8056, St. Louis, MO 63110
E-mail contact: rgovinda@dom.wustl.edu

Epidermal Growth Factor Receptor Inhibitors

It is estimated that nearly 16% of advanced stage nonsquamous lung carcinomas carry EGFR gene mutations.[8] Mutations in EGFR often result in the constitutive activation of several downstream signaling pathways leading to cellular proliferation. Specific mutations in the EGFR tyrosine kinase (TK) domain have been associated with responses to EGFR TK inhibitors such as gefitinib or erlotinib.[9] Preclinical studies have shown that the EGFR pathway is activated in tumors after radiation.[10–12] Addition of EGFR inhibitors could potentiate responses to radiation therapy.[13,14]

Monoclonal Antibodies

Cetuximab

It is hypothesized that monoclonal antibodies such as cetuximab, nimotuzumab, and panitumumab bind with the extracellular portion of the EGFR and inhibit pathway activation by blocking receptor dimerization.[15] The efficacy of combining these molecules with radiation therapy for the management of locally advanced NSCLC is being actively investigated. In the NEAR (NSCLC Erbitux and Radiotherapy) trial, 30 patients deemed "unfit" or unwilling to receive concurrent chemoradiation were treated with cetuximab (loading dose of 400 mg/m^2 intravenously on day 1, followed by 7 weekly doses of 250 mg/m^2) during concurrent radiation with 66 Gy, fol-

1525-7304/$ - see frontmatter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.clc.2013.03.005

Table 1 Cetuximab Based Clinical Trials in the Setting of Locally Advanced Non–Small-Cell Lung Cancer

Trial	Size	Use of Agent (Regimen/Phase)	Radiation Dose	Overall Survival in Months	Progression-Free Survival in Months
NEAR[16]	30	Concurrent radiation Cetuximab continued after radiation	66 Gy	19.6	8.5
N 0422[17]	57	Concurrent radiation	60 Gy	15.1	7.2
Swedish Lung Cancer Study Group[19]	71	Concurrent radiation (following induction chemotherapy)	68 Gy	17	NR
SCRATCH[18]	12	Concurrent radiation	64 Gy	NR	NR
Kotsakis et al[20]	38	Concurrent radiation With consolidation chemotherapy	73.5 Gy	17.1	9.3
RTOG 0324[21]	87	Concurrent chemoradiation With consolidation chemotherapy	63 Gy	22.7	NR[a]
CALGB 30407[23]	101	Concurrent chemoradiation (followed by consolidation with pemetrexed)	70 Gy	25.2	12.3

Abbreviations: CALGB = Cancer and Leukemia Group B; NEAR = NSCLC Erbitux and Radiotherapy; RTOG = Radiation Therapy Oncology Group.
[a] Progression failure rate of 55.2% at 24 months.

lowed by 13 weekly cycles of cetuximab.[16] An overall response rate of 63% was reported by the investigators. The median overall survival in this study was 19.6 months with a median progression-free survival of 8.5 months. Although differences in the stage (IIIa vs. IIIb) or histology did not seem to significantly influence patient survival in this trial, the investigators reported a trend favoring adenocarcinoma. In a similar US multicentric phase II trial (N 0422) that set out to examine the role of therapy with cetuximab alone, 57 patients (aged ≥ 65 years or with ECOG [Eastern Cooperative Oncology Group] performance status of 2) received cetuximab during concurrent radiation with 60 Gy.[17] The median survival and time to cancer progression in this study population were 15.1 and 7.2 months, respectively.

Regimens combining cetuximab with conventional chemoradiation were investigated in 4 clinical trials. The combination of cetuximab and thoracic radiation (64 Gy) after induction with 4 cycles of platinum-based chemotherapy was evaluated in a small phase I study (SCRATCH).[18] In this trial, 8 of the 12 patients (75%) enrolled were alive at the end of first year. The Swedish Lung Cancer Study Group trial was a multicentric phase II trial in which patients received 2 cycles of induction chemotherapy with cisplatin and docetaxel.[19] Cetuximab treatment was started one week prior to the 68-Gy course of radiation therapy, at an initial dose of 400 mg/m^2 followed by a weekly maintenance dose of 250 mg/m^2. The median survival was 17 months among 71 patients with inoperable locally advanced NSCLC who participated in this trial. Kotsakis and colleagues conducted a phase II study to investigate the effect of cetuximab in locally advanced NSCLC.[20] Thirty-eight patients who were deemed eligible to participate in this trial received cetuximab along with thoracic radiation, followed by consolidation chemotherapy. The median overall survival and progression-free survival were 17.1 and 9.3 months, respectively, with a favorable progression-free survival trend (P = .07) in patients whose tumors were positive for EGFR according to fluorescent in situ hybridization (FISH) analysis.

The Radiation Therapy Oncology Group (RTOG) 0324 conducted a phase II study in which 87 patients received cetuximab combined with weekly carboplatin-paclitaxel and 63 Gy of radiation.[21] After concurrent chemoradiation, patients also received consolidation chemotherapy. The median survival was 22.7 months and the response rate was 62%. At 24 months, the progression failure rate and survival rate were 55.2% and 49.3%, respectively. These promising results with cetuximab are being investigated further in the phase III setting in the RTOG 0617 trial. The study was initially designed to investigate the role of cetuximab with conventional dose radiation (60 Gy) chemoradiation and high dose radiation (74 Gy) chemoradiation. The high-dose radiation arms of the trial were closed to accrual after the demonstration of futility in an interim analysis.[22] However, the role of cetuximab is still being evaluated as planned, and results are awaited. The Cancer and Leukemia Group B (CALGB) conducted a randomized phase II trial (CALGB 30407) to study 2 novel chemotherapy regimens in patients with locally advanced lung cancer.[23] CALGB 30407 randomized 101 eligible patients to receive 70 Gy of radiation therapy with concurrent carboplatin and pemetrexed with or without cetuximab. Patients in both arms received consolidation therapy with 4 cycles of pemetrexed. The median overall survival among the 53 patients in the cetuximab arm was 25.2 months with a median failure-free survival of 12.3 months. The median overall survival and failure-free survival in patients who did not receive cetuximab were 21.2 and 12.6 months, respectively. Although the randomized study was not designed to assess the superiority of either regimen, a higher overall survival rate at the end of 18 months was reported in the non-cetuximab arm (58% vs. 54%). Survival outcomes in these cetuximab-based trials (Table 1[16–21,23]) compare favorably with outcomes reported in trials investigating other traditional chemoradiation regi-

Download English Version:

https://daneshyari.com/en/article/5882736

Download Persian Version:

https://daneshyari.com/article/5882736

Daneshyari.com